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October 14, 2003

VIA FEDERAL EXPRESS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 00N-1484
Comments on Proposed Rule: Safety Reporting Requirements for Human Drug and Biological Products

Dear Sir/Madam:

On behalf of our clients Luitpold Pharmaceuticals, Inc. ("Luitpold"), and its wholly owned subsidiary, American Regent, Inc. ("American Regent"), we hereby submit these comments in response to the Proposed Rule: Safety Reporting Requirement for Human Drug and Biological Products, Docket Number 00N-1484, published in the Federal Register on March 14, 2003 (68 Fed. Reg. 12406) ("Proposed Rule").

Luitpold, located at One Luitpold Drive, Shirley, New York, 11967, is a manufacturer and American Regent is a distributor of human drug products, primarily injectable drug products including many products used as diluents with other drug products. Luitpold and American Regent will be referred to as "Luitpold" for purposes of brevity.

Luitpold has the following comments regarding the following sections of the Proposed Rule:

1. Proposed 21 C.F.R. §§ 310.205(a), 312.32(a), 314.80(a), and 600.80(a)

A. Definition of "SADR"

The Proposed Rule creates a new term for adverse drug reactions - Suspected Adverse Drug Reaction ("SADR"). SADR means a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product

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caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out.

The acronym usage and definition for Suspected Adverse Drug Reaction ("SADR") is, Luitpold believes, misleading and confusing. Luitpold believes it should be Questionable Adverse Drug Reaction ("QADR"). According to the proposed definition, "no one can be sure if a response to a product is an SADR unless one is sure that the product did not cause the response."[1] As such, such a reaction is questionable upon initial reporting, and remains so unless and until full data information is retrieved. "Suspected" implies that causation is more likely involved, when the intent of the rule is to require reporting of any adverse drug reaction that cannot be ruled out resulting from the use of the drug product, even if at most questionable. Luitpold believes that QADR is, therefore, a more appropriate term.

B. Definition of "A Life Threatening "SADR"

The proposed definition for "a life-threatening SADR," that is"any SADR that places the patient or subject, in the view of the investigator or sponsor . . .," should be modified to include an independent contractor. Thus, the proposed definition should be "any SADR that places the patient or subject, in the view of the investigator or sponsor/contractor . . .".

C. Serious SADR, Nonserious SADR, and SADR with Unknown Outcome

According to the Proposed Rule, "if the outcome for an SADR is not known, a determination of serious cannot be made." Luitpold believes that an adverse reaction should be considered questionable if it has an unknown outcome. It would be proper to call it a QADR until causality is assigned. A reported reaction with no outcome should remain a QADR.

D. Foreign Reactions - Serious/Labeled

Presently, only serious, unlabeled (unexpected) foreign reactions need to be reported as expedited reports. The new proposal would expand this to include serious, labeled (expected) foreign reactions as well - that are considered "always expedited reports." Some of the conditions that require "always expedited reports" are common conditions in which a drug is used, and therefore the use of a drug may be associated with the condition. This could cause many ADR's to be reported where the only association is the use of a drug product where the patient already had the condition. This will, if implemented, create a significant increase in workload for both pharmaceutical

1 68 Fed. Reg. at 12417.

manufacturers and the FDA with little benefit, as the quality of the information received may be decreased (i.e., "active query" is more difficult and translations may be necessary for supportive documentation for foreign reports). The Proposed Rule inadequately evaluates the paperwork burden associated with implementation of this proposal. It, in Luitpold's opinion, should be withdrawn.

E. Definition of "Contractor"

Under proposed Sec. 314.80(a), the term ``contractor'' is defined as persons (e.g., manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant. Under proposed Sec. 600.80(a), the term ``contractor'' is defined as persons (e.g., manufacturer, joint manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant (includes participants involved in divided manufacturing).

The proposed contractor responsibility should be withdrawn, as it is too complex to be considered. The definition of "contractor" is too broad. As written this could include PBAs, dialysis centers, hospitals, advertising agencies, shipping companies – anyone the applicant has a contract with.

The proposed guideline would add yet another timeline, as contractors must submit safety reports for all SADRs (both serious and non-serious) and medication errors to the applicant within (5) calendar days and the additional burden to manufacturers of obtaining all needed information as the reports from the "contractors" need not contain even a minimum data set. Additionally, pharmaceutical manufacturers would need to have auditing procedures in place for "contractors".

All of the above create unnecessary and burdensome new requirements that Luitpold believes should be withdrawn.

F. Definition of "Medication Error"

The Proposed Rule defines a "medication error" as:

> Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare product, procedures, and systems including: prescribing; order communication; product labeling; packaging, and nomenclature;

compounding; dispensing; distribution; administration; education; monitoring; and use.

The proposed definition is overly broad. It places the responsibility of reporting, and therefore the responsibility for "potential" corrective action, upon the shoulders of the pharmaceutical industry, which has no authority to make recommendations or implement changes where medication errors are being made - in the place where healthcare, including the administration of drug products, is administered.

In all three (3) areas: "Medication Error", "Actual Medication Error" and "Potential Medication Error" reports have to be generated whether or not a patient actually received the medication. Luitpold believes this will be an impossible task given the number of practice sites (physician offices, pharmacies, hospitals, clinics, and many other healthcare settings) and the number of practitioners/prescribers (physicians, dentists, podiatrists, nurses, pharmacists, physician assistants, consumers and patient etc.). The follow-up needed for each report would have the industry grind to a halt given the current level of staffing. The additional personnel required to comply with this section of the Proposed Rule will increase the cost of healthcare tremendously at every level without any benefit to the healthcare community as a whole. It should be reconsidered.

G. Responsibility for Reporting Medication Errors

The Proposed Rule further does not adequately explain why this problem should be the responsibility of the pharmaceutical industry.

Luitpold agrees that there are too many medication errors in the US each year. However, better education of healthcare providers and better procedures to prevent these errors in the place where medication errors are made is, Luitpold believes, the correct action to take. The best place to prevent medication errors is at the lowest level possible and should involve the caregivers: medication prescribers, pharmacists and medication dispensers, medication administrators and lastly the consumer/patients themselves.

There are many other agencies at the national (USP, AMA, ASHP, etc.), state (Professional Licensing Boards, Office of Professional Discipline, State Professional Societies), as well as the private sector Consumer/Patient Advocacy Groups (AAKP, ADA, ACS, etc.) and Practice Sites (Hospitals, Clinics, Group Practices, etc.) that have the legal, professional or ethical responsibility to monitor medication and other errors and take the necessary corrective action to prevent future occurrences.

Luitpold believes the real issues are what is a medication error, who committed it and who should report it. HIPAA prevents pharmaceutical companies from dealing with patients (e.g., accessing telephone numbers of patient from provider). The reporting requirement should rest totally on the clinician or institutional pharmacist at the location of the event.

Again the best way to reduce medication errors is to prevent them at the patient care level and require the institutions where they occur to report them.

H. Medication Errors - "Grandfathered" and ANDA Products

Luitpold manufactures a number of grandfathered and ANDA'd products which have been marketed for many years. The indications and dosages that are in "approved and official" labeling for the products is often outdated and does not represent the current standard of medical practice.

The Proposed Rule would require the submission of a medication error report on "an inappropriate dose," even in cases where due to off-label use the dose administered represents the current standard of medical care. The Proposed Rule should be amended to clarify that a medication error report is not required in such a case.

I. Definition of "Full Data Set"

Under the Proposed Rule, a "full data set" for a postmarketing individual case safety report would include:

> Completion of all the applicable elements on FDA Form 3500A (or the Vaccine Adverse Event Reporting System (VAERS) form for proposed § 600.80(a)) (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADRs) including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error).

Luitpold believes that "completion of all applicable elements in the reporting form" is not an adequate definition of "full data set," and that the Proposed Rule should be amended to provide each element of what is considered the "full data set."

2. Proposed §§ 312.32(b), 314.80(b), and 600.80(b)

FDA proposes to amend § 312.32(b) such that it would require sponsors to review all information relevant to the safety of a drug under investigation obtained or received by the sponsor from any source, *including in vitro studies*. Furthermore, once the Sponsor/Contractor provides to the Agency its "animal and in vitro studies, emails, and reports from foreign regulatory authorities" it is concerned this additional information would become available to the public via the Freedom of Information Act. Luitpold questions why this additional data is significant and need be reported. The Agency should explain the need for this additional data, what use it will be put and how it will deal with the data vis-à-vis the FOIA, before implementing such a requirement. Otherwise Luitpold believes this proposed requirement should be withdrawn.

3. Proposed § 312.32(c)(2)

Currently, FDA requires sponsors to notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of an investigational drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. FDA is proposing to amend this section such that it reads:

> The sponsor must also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the sponsor of the minimum data set for the unexpected fatal or life-threatening SADR.

Luitpold believes that reporting be made as outlined for unexpected or life-threatening QADR where causality is assigned to drug (exclude minimal datasets where causality and assignment can be determined). This reporting should be limited to seriousness or have limited datasets. Non-serious events should only be filed with annual reports or PSURs.

A. "Cannot Be Ruled Out"

The Proposed Rule changes the definition of SADR, including those in premarketing studies, from one "associated with" to "cannot be ruled out." Luitpold believes that this change will essentially require all events to be reported unless one can affirmatively prove otherwise, which is impossible. This lack of flexibility, Luitpold believes, will mean that for any unexpected adverse event in a premarketing study, the study will need to be unblinded. If this occurs, the number of patients enrolled in clinical trials will need to be increased in order to reach the required sample size. It may also mean that sicker patients are removed from further analysis, changing the quality of

information generated in clinical studies. For these reasons, Luitpold opposes this proposed change.

4. Proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv)

Under the Proposed Rule, manufacturers must report to FDA each SADR, received or otherwise obtained, whether foreign or domestic, that is the subject of an "always expedited report." These reports must be submitted to FDA as soon as possible but no later than 15 calendar days after receipt by the manufacturer of the minimum data set for the report. Luitpold questions why the "always expected report" list is necessary.

The requirement in the Proposed Rule is, Luitpold believes, inconsistent with ICH guidelines. The "ICH HARMONISED TRIPARTITE GUIDELINE CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING - E2A" state:

> Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

With the above in mind, Luitpold questions why is the "always expedited list" necessary. If an adverse reaction is either more specific or more severe than the labeling (i.e., the list of expected reactions) then it is already by definition an "unexpected" reaction and would be reported as such. An "always expedited" list is redundant.

Additionally, if one of the events in the list of "Always Expedited Reports" is the indication for the use of the drug, it would make little sense to require this event to be an "always expedited report."

5. Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A)

The Proposed Rule requires manufacturers and applicants to submit to FDA, if available, a copy of the autopsy report if the patient dies. If an autopsy report is not available, the Proposed Rule requires manufacturers and applicants to submit to FDA a death certificate. The Proposed Rule requires that manufacturers and applicants use "active query" to obtain the documents required to be submitted.

While Luitpold does not question the potential value of such information, the problem is whether anyone will provide such supporting data to the Sponsor/Contractor. Given the fact that such supporting documentation, such as autopsy reports are limited, greatly delayed, and not public documents, it is questionable how much of such information will be readily available. Furthermore, while it is understood that HIPAA and many similar laws permit such reporting for purpose of adverse event reporting to FDA, given the complexity of such requirements, for practical purposes, it is questionable how much of this information will be actually available and, therefore, questionable how much fruitless "active query" will be required of manufacturers. Luitpold believes the FDA should clarify this requirement in any final rule. It should also limit access to any supporting data, such as death certificates on patients or subjects without required consent from the family.

6. Proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii)

The Proposed Rule would amend FDA's postmarketing periodic safety reporting regulations by changing the requirements for Periodic Safety Update Reports (PSURs) to include additional data. The PSUR would now be required to contain a number of appendices. One such appendix, called "Lack of Efficacy Reports," would contain an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug or biological product.

Luitpold questions the need for and value of such a report, given the problem in determining, for example, lack of efficacy with cancer drugs or diuretics that do not product diuresis, or antibiotics that do not show lysis of fever. The biologic mechanisms cannot be accurately predicted or accounted for in such a report, and its usefulness and accuracy is, therefore, questionable. Luitpold believes the FDA should reconsider the need for this type of report and withdraw this proposal.

7. Other Comments - Diluents

As indicated above, Luitpold manufactures a number of diluents, such as Sodium Chloride Injection, Sterile Water for Injection, and other diluents. These products are frequently contract manufactured for use in a kit containing the drug product of another manufacturer. They are also frequently used with lyophilized products in settings such as clinics, hospitals and other healthcare settings.

The Proposed Rule does not adequately address the reporting requirements and obligations where a diluent is used with the drug product of another company. Is the diluent manufacturer responsible for reporting a medication error which occurs with use of a product manufactured by another company, in which its product is mainly a diluent?

When an adverse event occurs with a lyophilized product that requires dilution, who is responsible for ADR reporting, active query and the like? Luitpold believes the Proposed Rule should be amended to clarify these requirements and make it clear that the obligation is not on the diluent manufacturer, but the manufacturer of the other drug product.

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Luitpold respectfully requests that the rule be amended and clarified as suggested in these comments.

Sincerely,

SONNENSCHEIN NATH & ROSENTHAL LLP

By:

Peter S. Reichertz

Filed in triplicate